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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/462,635	SCHMIDT ET AL.	
	Examiner	Art Unit	
	Jeanine A Enewold	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *10 April 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Priority

1. This application is a 371 of PCT/GB98/02043, filed July 13, 1998. This application also claims priority to three foreign documents.

Drawings

2. The drawings have been approved by the draftsman.

Specification

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-25 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for categorizing nucleic acid but the final process step is isolating nucleic acid which hybridizes to an oligonucleotide sequence which has a pre-determined recognition

sequence. Therefore the claims are unclear as to whether the method is a method of categorizing nucleic acid or isolating nucleic acid. Furthermore, it is unclear whether these two terms, categorizing and isolating are equivalents. It is believed that categorizing is broad enough to encompass not only isolating, but also characterizing, sorting nucleic acids or other manipulations of nucleic acids.

B) Claims 1-25 are indefinite over the recitation "producing a nucleic acid population by action of an endonuclease on double-stranded nucleic acid" because it is unclear whether the double stranded nucleic acid has been merely cut by an endonuclease or whether the endonuclease has had another effect on the double stranded nucleic acid such that a population is generated. Therefore, the metes and bounds of the claimed invention are unclear.

C) Claims 1-25 are indefinite over the recitation "a pre-determined recognition sequence" because in essence all primers, probes and other oligonucleotides which hybridize to a nucleic acid have a site of recognition which is complementary to the oligonucleotide. Thus, it is unclear what further limitations the recitation "a pre-determined recognition sequence" implies. Many oligonucleotides may be forced to "hybridize" to the nucleic acid sequence by varying conditions, thus, this limitation carries little weight.

D) Claims 1-25 are indefinite over the recitation "one or more different recognition sequences being represented in the oligonucleotide sequences" because it is unclear whether a single oligonucleotide sequence contains more than one

recognition sequence, or whether the set of oligonucleotide sequences is composed of oligonucleotides with different recognition sequences.

E) Claims 13-22 are indefinite over the recitation "wherein those nucleic acids are isolated both terminals of which correctly hybridize to an oligonucleotide sequence" because it is unclear whether only nucleic acids which have been isolated at both ends are selected. The recitation "wherein those nucleic acids" is unclear since the nucleic acids being referred to are ambiguous. The grammar of the claim makes the interpretation very unclear. It is possible a word is missing which would clear up the issue. However, it is not readily apparent what word might be missing.

F) Claims 13-22 are indefinite over the recitation "terminals" because "terminals" is not an art recognized term. While the termini of the DNA molecule is a recognized term, it is unclear what "terminals" include.

G) Claims 14-22 are indefinite because it is unclear whether "in a first step", as recited in line 2, is meant to read the first step such that the method steps of Claim 14 precede the method steps of Claim 1, or whether the method steps of Claim 14 are meant to be performed following the method steps of Claim 1. If the former is intended it is unclear how the single stranded nucleic acid then is digested such that double stranded regions are generated. Based upon the drawings provided in the instant disclosure is appears that Claim 14 is performed after the nucleic acids have been "categorized", however the language of Claim 14 does not make this readily apparent since Claim 1 already isolates the selected nucleic acids.

H) Claims 19-22 are indefinite over the recitation "the recognition sequence of the first and second set of oligonucleotide sequences" because it is unclear whether the oligonucleotide sequences are referring to the "one or more oligonucleotide sequences" as taught in Claim 1, lines 4-5, or whether the "oligonucleotide sequences" are referring to the oligonucleotide sets established in Claim 14 for the amplification reaction. Since the claim recites "the recognition sequence" which is only provided for in Claim 1, not Claim 14, it is unclear exactly which recognition sequences and oligonucleotides are being discussed.

I) Claims 19-22 are indefinite over the recitation "prior to performing the first step" because it is unclear whether the method of Claims 19 and 20 are directed to prior to performing the first step in the entire assay or whether the claims are directed to prior to performing the first step of Claim 14.

J) Claims 21-22 are indefinite because it is unclear how if all of the sequences and combinations were represented in the 16 wells of Claim 19 or the 256 wells of Claim 20, new combinations give new wells. It is unclear whether these additional wells are merely additional trials since is appears that all combinations were previously proposed.

K) Claims 26-36 are indefinite over the recitation "wherin the adaptors comprise nucleic acid having double stranded primer protion of a known sequence" because it is unclear what a primer portion of the adaptor is. It is unclear whether there is a defined region which a primer is able to bind and thus extend, whether the entire adaptor may be the primer portion, or whether only the double stranded region is the primer portion.

L) Claims 26-36 are indefinite over the recitation "a single-stranded portion of a pre-determined length, either each single-strnaded portion of each nucleic acid in the adaptors having the same pre-determined sequence of all possible sequences of the single-stranded portion being represented in the adaptors" because it is very confusing. It is unclear whether the single stranded region on the adaptor is all the same sequence for all of the adaptors or whether the single stranded region may have more than the single sequence, or whether all of theses single-stranded regions are different from all of the other adaptors.

M) Claims 26-36 are indefinite over the recitation "the second sequence is the same sequence as the single-stranded portion of the adaptors of all possible second sequences of the same length as the single-stranded portion of the adaptors" because it is unclear what is in fact being claimed. It is clear that there are three regions to the oligonucleotide sequence, however it is very confusing the limitations of each of these regions.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1-13, 25-28 and 32-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Sibson (WO 94/01582, January 1994).

Sibson teaches a method of categorizing nucleic acid. Sibson teaches a method which comprises producing a nucleic acid population by action of a endonculease on double-stranded nucleic acid, such that each nucleic acid in the nucleic acid population has a double stranded portion (pg. 13, step a). Suitable restriction endonucleases which recognize single stranded DNA and which also leave a cleaved sequence overhang when cutting double stranded DNA include BstNi, DdeI, HgaI, HinfI and MnlI (pg. 11, lines 26-27)(limitations of Claim 3). Preferred reagents or Class II restriction endonucleases that cleave sites which are asymmetrically spaced across two strands of DNA and the specificity of which is not affected by the nature of the bases adjacent to a cleavage site (pg. 16, lines 1-3)(limitations of Claim 2, 6 25, and 36). Examples of these endonucleases may leave a 5 base overhang starting 5 bases from the cut site or cut 7 bases away leaving only a 1 base overhang (pg. 12, lines 2-4)(limitations of Claim 35). The nucleic acid population is contacted with an adaptor to ligate the adaptor to a terminal of each nucleic acid in the nucleic acid population such that the adaptor comprises a double stranded primer portion having a known base sequence and a single stranded portion complementary to the known sticky end of the nucleic acids in the nucleic acid population (pg. 13, step b)(limitations of Claim 4). Sibson teaches that the adaptor molecules preferably comprise oligonucleotides in which single stranded ends of known nucleotide composition are present which is complementary to a

predetermined nucleic acid end sequence or end nucleotide so as to permit linkage (pg. 9, lines 15-21)(limitations of Claim 4 and 7). "At least some of the adaptor molecules of the present invention can be structured so as to permit separation of the present process by immobilizing adaptored products on a solid phase (pg. 10, lines 21-25). A population of adaptors may be used simultaneously such that the total possible adaptor molecules required for "adaptoring" all possible sequence types (pg. 14, lines 15-16). Adaptors may carry biotin to allow selective separation of the desired adaptor molecules (pg. 19, lines 1-3). Sibson teaches that it is preferred that adaptors covering all possible reactions in a chosen subset of sequence be present, because then the opportunity for fragments in the chosen subset to ligate to each other is minimized (pg. 20, lines 21-25)(limitations of Claim 8).

Sibson also teaches contacting the nucleic acid population with one or more oligonucleotide sequences. Using primers of preselected sequence, effectively enables one or more predetermined subset(s) of sequence to be selected (pg. 11, lines 3-5). Sibson further teaches isolating nucleic acid which correctly hybridizes to an oligonucleotide sequence by capturing the oligonucleotide sequence on a solid phase (pg. 13, step c). The oligonucleotide sequence has a predetermined recognition sequence. The nucleic acid is categorized by its ability to correctly hybridize to oligonucleotide sequences having the recognition sequence. The recognition sequence is situated such that it recognizes a sequence in the double-stranded portion of the nucleic acid. Finally, one or more different recognition sequences is represented in the oligonucleotide sequence. Sibson discloses a kit comprising adaptors, endonuclease,

FoKI, and oligonucleotide sequences used as PCR primers (pg. 23, para. 2 and Claims 29-34)(limitations of Claim 26-28 and 32-35). The PCR primers comprise in some embodiments a sequence complementary to the core sequence of the adaptors ('first sequence") and may preferably extend by one or more specific extra bases into the adaptored fragment ('third sequence")(pg. 28, lines 25)(limitations of Claim 9-11). This implies that the oligonucleotide sequences also contain the sequence of the single stranded portion of the adaptor ("second sequence")(limitations of Claim 5). Thus, these primers contain all the technical features of the oligonucleotide sequences claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 14-22, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sibson (WO 94/01582, January 1994) in view of Dynal Catolog (1995).

Sibson teaches a method of categorizing nucleic acid. Sibson teaches a method which comprises producing a nucleic acid population by action of a endonculease on double-stranded nucleic acid, such that each nucleic acid in the nucleic acid population has a double stranded portion (pg. 13, step a). Suitable restriction endonucleases

which recognize single stranded DNA and which also leave a cleaved sequence overhang when cutting double stranded DNA include BstNi, DdeI, HgaI, HinfI and MnlI (pg. 11, lines 26-27)(limitations of Claim 3). Preferred reagents or Class II restriction endonucleases that cleave sites which are asymmetrically spaced across two strands of DNA and the specificity of which is not affected by the nature of the bases adjacent to a cleavage site (pg. 16, lines 1-3)(limitations of Claim 2, 6, 25, and 36). Examples of these endonucleases may leave a 5 base overhang starting 5 bases from the cut site or cut 7 bases away leaving only a 1 base overhang (pg. 12, lines 2-4)(limitations of Claim 35). The nucleic acid population is contacted with an adaptor to ligate the adaptor to a terminal of each nucleic acid in the nucleic acid population such that the adaptor comprises a double stranded primer portion having a known base sequence and a single stranded portion complementary to the known sticky end of the nucleic acids in the nucleic acid population (pg. 13, step b)(limitations of Claim 4). Sibson teaches that the adaptor molecules preferably comprise oligonucleotides in which single stranded ends of known nucleotide composition are present which is complementary to a predetermined nucleic acid end sequence or end nucleotide so as to permit linkage (pg. 9, lines 15-21)(limitations of Claim 4 and 7). "At least some of the adaptor molecules of the present invention can be structured so as to permit separation of the present process by immobilizing adaptored products on a solid phase (pg. 10, lines 21-25). A population of adaptors may be used simultaneously such that the total possible adaptor molecules required for "adaptoring" all possible sequence types (pg. 14, lines 15-16). Adaptors may carry biotin to allow selective separation of the desired adaptor molecules

(pg. 19, lines 1-3). Sibson teaches that it is preferred that adaptors covering all possible reactions in a chosen subset of sequence be present, because then the opportunity for fragments in the chosen subset to ligate to each other is minimized (pg. 20, lines 21-25)(limitations of Claim 8). Sibson also teaches contacting the nucleic acid population with one or more oligonucleotide sequences. Using primers of preselected sequence, effectively enables one or more predetermined subset(s) of sequence to be selected (pg. 11, lines 3-5). Sibson further teaches isolating nucleic acid which correctly hybridizes to an oligonucleotide sequence by capturing the oligonucleotide sequence on a solid phase (pg. 13, step c). The oligonucleotide sequence has a predetermined recognition sequence. The nucleic acid is categorized by its ability to correctly hybridize to oligonucleotide sequences having the recognition sequence. The recognition sequence is situated such that it recognizes a sequence in the double-stranded portion of the nucleic acid. Finally, one or more different recognition sequences is represented in the oligonucleotide sequence. The PCR primers comprise in some embodiments a sequence complementary to the core sequence of the adaptors ('first sequence") and may preferably extend by one or more specific extra bases into the adaptored fragment ('third sequence")(pg. 28, lines 25)(limitations of Claim 9-11). This implies that the oligonucleotide sequences also contain the sequence of the single stranded portion of the adaptor ("second sequence")(limitations of Claim 5). Thus, these primers contain all the technical features of the oligonucleotide sequences claimed. Sibson teaches that the number of subsets performed when the adaptors are specific for two bases is 256 (pg. 31). Furthermore, Sibson teaches all possible combinations are used. Sibson

teaches that "in a subsequent stage of preferred process of the invention, a further degree of selection can be achieved by coping or amplifying only selected subsets of the subset of specifically adaptored nucleic acid fragments" (pg. 28, lines 11-20). Sibson teaches that the members of sorted populations form unique and discrete sets that could be used more conveniently to identify fragments of interest by a suitable hybridization probe (pg. 55, lines 15-20).

Although Sibson discloses subsequent selection of the nucleic acids, Sibson does not specifically teach the generation of single-stranded probes as taught by the instant disclose in Claims 14-18.

Further, while Sibson teaches that 256 subsets are present when the "recognition sequence" has two bases, Sibson does not explicitly teach that one base yields 16 different combinations.

However, Dynal teaches a method of generating and isolating non-immobilized single-stranded nucleic acid. Dynal teaches contacting a first set of oligonucleotide sequences, biotinylated primers, with the nucleic acid population. The single stranded primers hybridized, extended via PCR and then immobilized onto a Dynabead via the biotin (Figure 10.1)(limitations of Claims 15-18). The double stranded nucleic acid is denatured and the non-biotinylated immobilized species is removed. The immobilized single-stranded nucleic acid is the contacted with a random priming or a specific labeled primer, a second set of oligonucleotide sequence, and extended to form a double-stranded nucleic acid. The double stranded nucleic acid is the denatured and the resulting non-immobilized single stranded nucleic acid is isolated.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Sibson with the teachings of Dynal. The ordinary artisan would have been motivated to have performed the categorizing method of Sibson and subsequently performed the method of Dynal to synthesize single-stranded probes in order to generate probes of known sequences in which were identified by the categorization method of Sibson. Sibson teaches that the categorizing method is particularly adapted to facilitate sorting and investigation of rarer sequences in a population (pg. 8,lines 10-13). Thus, once the sequences have been identified by the categorization method of Sibson the ordinary artisan would have been motivated to have made the single stranded probes for the subsequent use in hybridization assays to identify the "rarer" nucleic acids in a sample as taught by Sibson. It would have been obvious to have categorized nucleic acids by the method of Sibson and further developed probes which would allow detection of the categorized samples for the expected benefit, taught by Sibson, that it would be easier than probing all possible fragments at once (pg. 55, lines 23-25). Based upon the indefinite nature of the claims as detailed in the 112/2nd paragraph discussion, the ordinary artisan would also have been motivated to have prepared the nucleic acids as taught by Dynal prior to the method of Sibson. The ordinary artisan would have been motivated to have amplified and generated nucleic acid from a sample for subsequent analysis in the categorization method. Moreover, it would be obvious to place these added reagents into the kit of Sibson for the ability to easily perform the assay. Thus, both

interpretations of the instant claims would have been obvious over Sibson in view of Dynal.

Additionally, the limitations of Claims 19-22 are obvious in view of the teachings of Sibson and Dynal. It would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Sibson to encompass the limitations of Claim 19-22. Sibson effectively taught that the number of combinations of specific adaptors with two base specificity to be 256 (pg. 31). The ordinary artisan would have realized that the teachings of Sibson also encompassed a single base specificity which would only have 16 different options based upon the analysis provided by Sibson (pg. 31, lines 20-30). Thus, the ordinary artisan would have been motivated to have prepared all of the possible combinations as taught by Sibson in the method of Sibson in view of Dynal for the expected benefit of categorizing all of the nucleic acids in the sample for further analysis.

7. Claims 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sibson (WO 94/01582, January 1994) in view of Dynal Catalog (1995) as applied to Claims 14-20 and 29-31 above and further in view of Hartley et al (US Pat 5,106,727, April 1992).

Neither Sibson nor Dynal specifically teach the incorporation of analogues into the oligonucleotides.

However, Hartley et al. (herein referred to as Hartley) teaches incorporating non-standard bases into random primers to reduce de novo synthesis.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Sibson in view of Dynal to include the non-standard bases as taught by Hartley for reducing the de novo synthesis. The ordinary artisan would have been motivated to have reduced the amount of de novo synthesis to obtain results representative of the categorized population as opposed to additional nucleic acid molecules.

Conclusion

8. No claims allowable over the art.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Deugau et al (US Pat 5,508,169, April 1996) teaches a method of digesting double stranded nucleic acids with Type IIS restriction enzymes, ligating the fragments to linkers which are representative of all the possible permutations.

.B) Kato et al (EP 0 735 144 A1, March 26, 1996) teaches a method for indexing categorizing of genes using restriction enzymes to digest nucleic acids, ligate adaptors containing biotin, isolating the nucleic acids and finally amplifying.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold
August 16, 2000

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800